

Epidemiology of Radiation-Induced Cancer

by Edward P. Radford*

The epidemiology of radiation-induced cancer is important for theoretical and practical insights that these studies give to human cancer in general and because we have more evidence from radiation-exposed populations than for any other environmental carcinogen. On theoretical and experimental grounds, the linear no-threshold dose-response relationship is a reasonable basis for extrapolating effects to low doses. Leukemia is frequently the earliest observed radiogenic cancer but is now considered to be of minor importance, because the radiation effect dies out after 25 or 30 years, whereas solid tumors induced by radiation develop later and the increased cancer risk evidently persists for the remaining lifetime. Current estimates of the risk of particular cancers from radiation exposure cannot be fully evaluated until the population under study have been followed at least 40 or 50 years after exposure. Recent evidence indicates that for lung cancer induction, combination of cigarette smoking and radiation exposure leads to risks that are not multiplicative but rather nearly additive.

I believe an important reason that radiation-induced cancer is especially pertinent to the discussion today is because it is frequently related to a definition of the acceptability of risk (1). Radiation provides a useful model of ways of evaluating risks from all environmental agents, because we have more information about health effects of radiation in human populations than we have for any other environmental agent of which I am aware (2). Thus it is critical that we look at the evidence relating radiation to cancer and discuss some of the problems that exist in interpreting the epidemiologic data.

I would like to begin by presenting some theoretical concepts which follow a point made by Upton (2). With respect to cellular effects of radiation on DNA, and we believe radiation carcinogenesis is at least associated with phenomena having to do with cellular DNA, if E represents an incremental effect of radiation, say, on cancer incidence, then we can express E as a function of dose D in an equation of the form,

$$E = (aD + bD^2) \exp \{ -\alpha D - \beta D^2 \} \quad (1)$$

where a , b , α and β are empirical constants. The first two terms are of a linear and quadratic form and relate mutagenic or carcinogenic probability

to radiation dose. Then there is an exponential term related to cell survival probability; for cancer to occur, the cell or cells transformed have to survive to lead to descendants which eventually form a cancer. The negative exponent means that as dose increases, survival decreases.

This mathematical formulation fits closely the experimental data presented by Upton (2). The ratio of the constant b to constant a , which I take to be about 0.01 when the dose D is in rads, is close to the value given by Upton for this ratio of the quadratic and linear component. For the exponential term also the ratio β/α is also about 0.01 for acute cell killing, again in agreement with Upton. With the assumption of these values, Eq. (1) takes the form

$$E = aD(1 + 0.01D) \exp - \{ \alpha D (1 + 0.01D) \} \quad (2)$$

when D is in rads.

If you plot this curve, with an assumption of 0.001 for α based on cell survival studies, you find that it is close to a straight line up to a dose of about 250 rads. It is actually slightly sigmoid because of the dose squared (bD^2) term, but the effect of the exponential term almost cancels out the effect of the quadratic term and the result comes out close to a straight-line relationship. If we apply classical radiobiological principles to dose-response curves, which Upton has so elegantly presented, Eqs. (1) and (2) are consistent with a large literature of theoretical and experi-

*Center for Environmental Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA 15261.

mental data. They also support the linear no-threshold approximation for definition of the dose-response relationship, such as for cancer induction.

In practice, some of the factors we have to consider in evaluating epidemiologic evidence of cancer risk from radiation exposure include: exposure conditions, special risks by age, application of the absolute risk versus the relative risk models, the latent period from exposure to onset of cancer, and finally the duration of the carcinogenic effects. These last two points are important because there has been, I think, a lot of confusion in the minds of many people about the duration of the effect, even by some who are quite knowledgeable about this subject. For example, from early studies that were carried out, especially on the Japanese A-bomb survivors, it was found that leukemia was the cancer that appeared first in excess. Subsequently, it became apparent that this effect of radiation, given in this case virtually instantaneously, was dying out, in that the excess leukemia was disappearing in the population. As of 1974, 30 years after the bombing, it had almost completely disappeared (3). In other words, the increased risk of leukemia rose approximately 2 years after the bomb, went through a maximum at about 8 to 10 years, and then has declined back again to the expected rate after 25 to 30 years.

Because leukemia showed the first significant increase in cancer risk in this population, it has received special attention for this reason. Other populations that have been studied, such as the British spondylitics mentioned by Dr. Upton, also showed very much the same kind of time course for leukemia (4). It turns out, however, that this time course for excess cancer is the exception, not the rule, and almost all other solid cancers being found in irradiated populations, including the Japanese A-bomb survivors, have much longer latent periods to onset, and have not shown a decline with time, at least up to the present. The indications are now that excess risk of nearly all other cancers will probably persist for the lifetime

of the population exposed. One of the most important conclusions that can be derived from this statement is the fact that when we add up all of the cancers that may be produced by radiation, those which come on much later and have a longer latent period to onset, such as cancers of the female breast, thyroid, lung, or intestinal tract, become much more important than leukemia. In fact, it is fair to say now that leukemia is a minor cancer produced by radiation. The principal reason for this is because of the difference in the duration of the effect. Individuals irradiated at, say, age 20 or 30, have a long life-span in which they subsequently can develop cancer, and the fact that excess risk of cancers other than leukemia presumably will not die out over time makes these cancers much more important in terms of a lifetime cancer risk. In view of these considerations, the degree of emphasis some people place on radiogenic leukemia is unwarranted.

To illustrate the long duration of cancer effects, Table 1 shows some recent data derived from a group of 1400 Swedish iron miners. Here observed and expected lung cancer deaths are given as a function of time after starting mining. These miners were exposed to quite low concentrations of radon daughters, the concentrations in these mines being very close to the standard currently in operation for U.S. miners. So these data give a preview of what we can anticipate from underground miners in the U.S. today if they are exposed at or near the current exposure limit.

As a function of years since they began underground mining, the observed versus the expected cases of lung cancer did not rise until 20 or more years after they began mining. At 50+ years there is still an excess, and furthermore, from 20 years to more than 50 years, the relative risk stays essentially constant. That is, the ratio of observed to expected cases shows no statistically significant difference over time. There is a 3.4-fold excess risk of lung cancer for the whole group, taken from 10 years after the beginning of mining. In other words, our current standard

Table 1. Lung cancer deaths by years since began underground; period of observation 1951-76.

Lung cancer deaths	Years since began underground						Total
	0-9	10-19	20-29	30-39	40-49	50+	
Observed	1	1	7	14	23	5	51
Expected, based on Swedish national rates	0.27	0.99	2.28	4.54	5.19	1.61	14.87
Observed/expected	3.71	1.01	3.08**	3.08**	4.44**	3.11*	3.43**
Lower confidence limit ($\alpha = 0.025$)	0.09	0.03	1.24	1.68	2.81	1.01	2.55
Upper confidence limit ($\alpha = 0.025$)	20.63	5.60	6.34	5.17	6.66	7.27	4.51

*Significant at 5% level.

**Significant at 1% level.

gives rise to approximately 3.4-fold risk of lung cancer compared to an unexposed population. The point I am making here is that the effect persists after long periods of time. The mean duration of work underground was about 20 years for these miners, so most of the group had stopped mining by 30 years after beginning, and therefore little or no further exposure took place after that time. Yet the risk is persisting out to 50 or more years.

Let us now consider some of the classic epidemiologic data on radiation-induced cancer in human populations. Figure 1 shows data on mortality from all cancers except leukemia plotted against radiation dose for the Japanese A-bomb survivors. These data were as of follow-up to 1974. Results for the two cities, Hiroshima and Nagasaki, are presented independently. A very long acrimonious tale hangs upon this particular graph, I can assure you. If a dose-response curve is fitted over all of the data points for Nagasaki, the slope is very different than that for Hiroshima, and this lower slope was considered to be

very important, even though it depended largely on the difference in the two cities at one single data point. If you fit only the lowest dose points which are somewhat stronger epidemiologically, there is little difference between the two cities. The difference was thought to be in the neutron component of the two bombs. The Nagasaki plutonium bomb was considered to have few neutrons, while the Hiroshima U-235 bomb was thought to have a significant neutron component. More recent evidence, just developed within the last year, indicates that in fact the 1965 dosimetry in Japan was wrong, and there was no significant amount of neutrons in Hiroshima after all, and therefore, that argument cannot be used to explain this difference.

Another important point to note is that this graph deals with cancer mortality. There has been some discussion at this symposium of the inaccuracy of mortality statistics. The major cancers that arise from radiation, such as breast, thyroid, and even lung cancer, are not well repre-

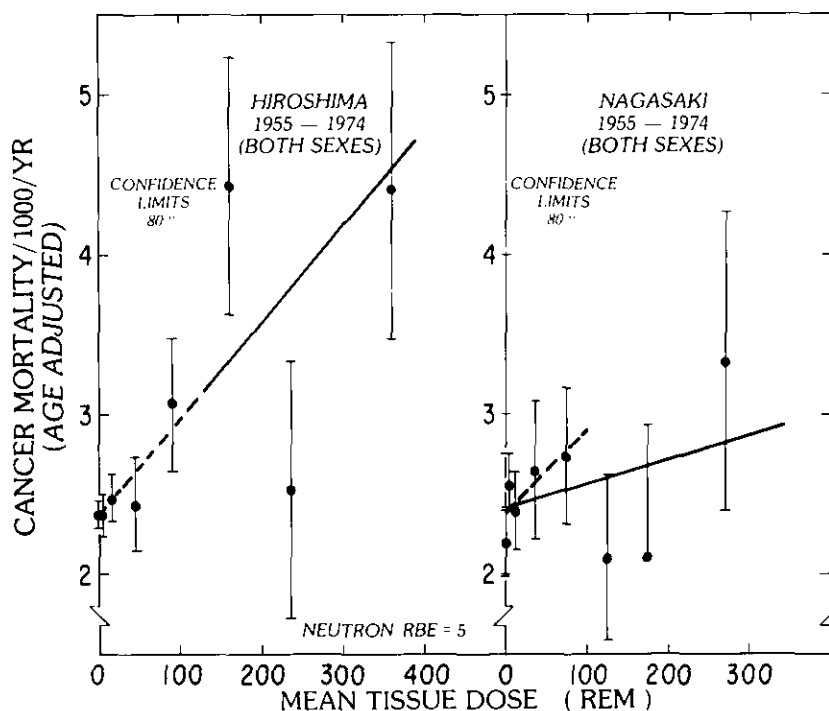


FIGURE 1. Mortality from all cancers except leukemia, Japanese A-bomb survivors, 1955-1974, both sexes combined: (left) Hiroshima; (right) Nagasaki. Ordinate: deaths per thousand per year age-adjusted to total population. Abscissa: mean tissue dose in rem derived from coefficients of Kerr, and on assumption that the neutron component in both cities had a constant RBE of 5. Vertical bars represent 80% confidence limits for individual points. Dashed lines show weighted linear regression applied to data below 100 rem. Reprinted by permission from Radford (5).

sented in these mortality data. For example, the reason that lung cancer mortality is uncertain is that in Japan the diagnosis of lung cancer on death certificates is really quite inaccurate, unlike in the United States. Autopsy comparisons among the A-bomb survivors have shown that almost one-half of the cases identified at autopsy are not correctly assigned to lung cancer on death certificates.

Fortunately, we have other data. Figure 2 is cancer incidence data from the tumor registries in the two cities for the period 1959–1970. In this case we find there is very little difference between the two cities. There is a slightly greater slope in Hiroshima compared to Nagasaki, but unlike the mortality results, the incidence data are reasonably consistent with the linear no-threshold dose-response curve in both cities. Granted, there are large error limits for the data points and from

these results one cannot distinguish a straight line from a slightly curved dose-response.

The results shown in these graphs are now made obsolete by the new dose estimates for the A-bomb survivors. Only recently I received from Dr. Loewe at the Livermore Laboratory a more detailed basis on which I could calculate how the old dose data would change with the new evidence. The principal effect is that the slope of the line in both cities will be higher, especially in Nagasaki, and nearly all the dose is now from γ -radiation in Hiroshima as well as in Nagasaki. Therefore, the cancer incidence results are strongly supportive of a similar dose-response for the two cities. Thus, the radiation-induced cancer effect is the same in the two cities, and we can now combine the data and improve the epidemiologic reliability of estimates of effect at low doses. I predict that by the final follow-up of this popula-

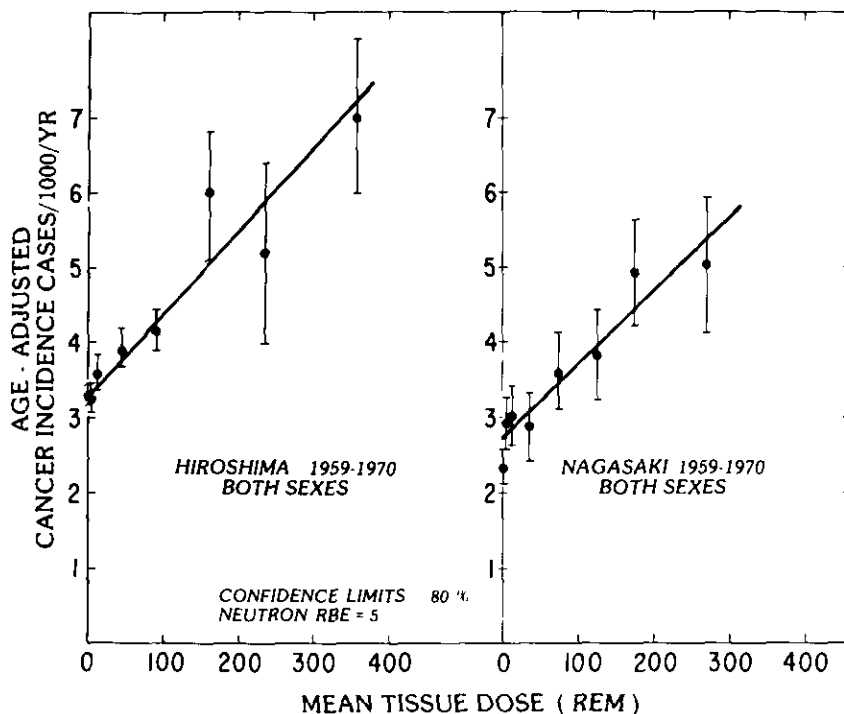


FIGURE 2. Cancer incidence for all cancers except leukemia, Japanese A-bomb survivors, 1959-1970, both sexes combined: (left) Hiroshima; (right) Nagasaki. Ordinate: incidence, cases per thousand per year age-adjusted to total population. Abscissa: mean tissue dose in rem as in Figure 1. Vertical bars represent 80% confidence intervals for individual points. The line drawn is the weighted linear regression, which fits all data points well, without the marked irregularity of high dose points seen in Figure 1. The population bases for the incidence and mortality studies are the same; the difference is dependent on mode of ascertainment of cases. Reprinted by permission from Radford (5).

tion, it will be possible to show a significant excess of cancer at about 10 rads γ -dose or perhaps less, because of the size of the study population and the fact we can now combine results from the two cities.

The leukemia data, again with the old 1965 dosimetry, show a slight upward curvilinearity in both cities, but because of the dose uncertainty the dose-response for leukemia will also have to be separately reevaluated. Nevertheless, the leukemia results were a main basis for the decision to use the linear-quadratic equation in the BEIR III report (5).

This evidence from the Japanese A-bomb survivors is important because of the fact that they have a range of doses and they also were a substantial sized population—about 48,000 actually exposed to more than minimal doses. Other data are available for comparison. Figure 3 shows the incidence of breast cancer in relation to radiation dose in four groups of women (6). For the A-bomb survivors, in the upper left-hand graph, a rather irregular dose response is found, but significant effects at relatively low doses are present. Note that both cities are combined in this study because no difference was found even with the previous dose estimates. On the upper right-hand graph were women irradiated during collapse

therapy for tuberculosis who received a breast dose as a result of multiple chest fluoroscopies. Exposure for these women was to repeated small doses: the average dose to breast tissue was estimated at 1.5 rads per fluoroscopy, and on average each woman had about 100 exposures. On the lower left are shown results for a group of women in New York who were given X-ray therapy for post-partum mastitis. In this case from one to four doses to the breast tissue was given. Finally the lower right graph is from a group of Nova Scotia women also given fluoroscopies for collapse therapy. In this case there is no estimate of dose, and the abscissa is presented simply as number of fluoroscopies.

The significant point from these studies illustrates another important factor in the use of epidemiology in the definition of risk, and therefore, as a basis for standard-setting, namely, replication of results. The risk coefficients derived from the three studies in which there are quantitative dose data are remarkably similar. Because these three studies, with γ - or X-ray exposures for very different reasons, and with different ethnic backgrounds and usual breast cancer rates, give closely similar radiation risk coefficients, considerable strength is added to the data for each.

Another important question is the strength of

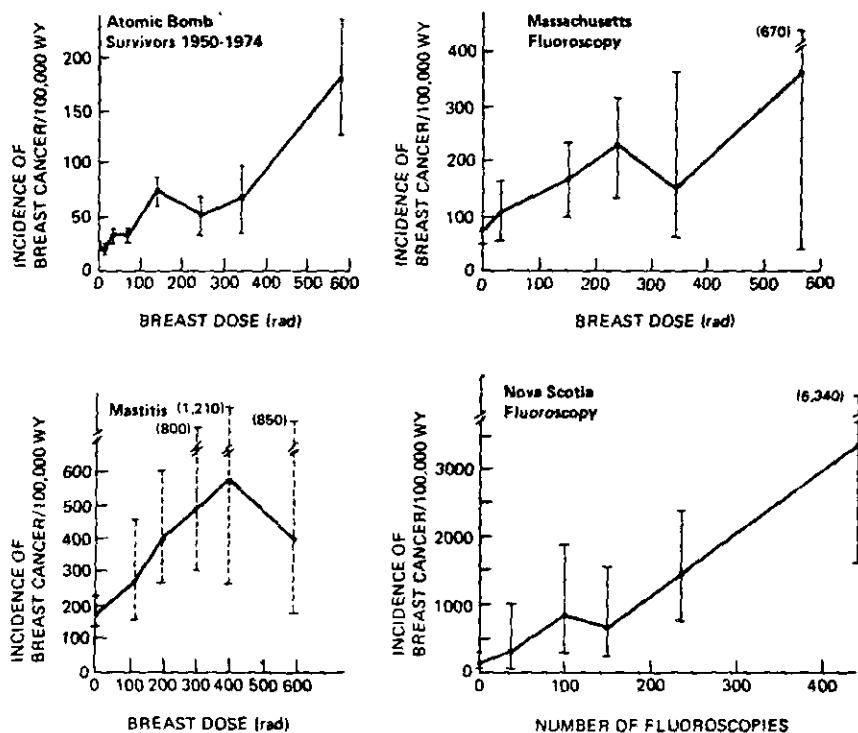


FIGURE 3. Incidence of breast cancer in relation to radiation dose. Reprinted with permission from Boice et al. (6).

data at low doses. For example, Modan's study of thyroid cancer in 10,000 Israeli children given X-ray treatments for ringworm of the scalp found evidence of thyroid cancer excess at less than 9 rads total dose to the thyroid (7). In the Swedish iron miners discussed above we have found doubling of observed over expected cases at cumulative dose of 27 working level months, a unit of cumulative dose of α -radiation from radon daughters, only about five times background for people exposed to indoor radon daughters at home. As some of you know, the question of radon daughters in houses is now becoming a major public health concern. We can, in other words, use epidemiologic methods to try to define the dose-response curve by working with groups exposed to radiation doses as low as we can conceivably demonstrate a significant effect. The effects investigated should involve the cancer types most sensitive to radiation.

Upton (2) emphasized that for γ rays and X-rays, spreading the dose out over time would perhaps be expected to reduce the effect. In the case of exposures to alpha radiation, spreading out the dose over time appears to increase the effect. Therefore the rate at which radiation exposure occurs is a variable modifying the carcinogenic potential.

Another point has to do with the question of synergism between two environmental agents. In the case of lung cancer, the cigarette smoking experience becomes important. One of the significant things we have been able to do in our study of Swedish iron miners has been to evaluate smoking independently. We have been able to calculate smoking-specific expected rates in this population. The risk per unit dose per million person years at risk is not greatly different for smokers and nonsmokers in this case. That is contrary to what people have generally been saying about radiation-induced lung cancer. It was said that the effect of smoking was multiplicative with the radiation exposure. My belief is the reason why we have found no multiplicative effect phenomenon is because we have much longer follow-ups than for most other mining populations exposed to radon daughters. Thus I believe that previous statements about the multiplicative effects of smoking may be epidemiologic artifacts of a short follow-up time. If the onset of radiation-

induced cancer in nonsmokers is delayed, then the risk could be strongly dependent on how long the people are studied.

Thus, effects of incomplete follow-up are a general problem in interpreting any epidemiologic study. For a disease like cancer, with a long time from initiation to expression, a final resolution of many issues relating exposure to cancer risk may require study of the population for nearly their lifetime. For example, the A-bomb survivors are far from having completed their lifetimes. Some of the current data indicate that if an individual were irradiated at age 20 he might have a lower risk than someone radiated at age 60. But if the projections found thus far apply, because the 20-year old has a longer life-span available, the actual lifetime risk is greater for the younger individual than it is for the older individual.

We are now in a position to predict, using life table techniques, how much lifetime risk of cancer will occur under various radiation exposure regimens. This permits the regulatory process to proceed with the best science we have today. There remain a number of assumptions that have to be made, but as follow-up studies extend in time, we should have good evidence on which to resolve the remaining questions. I believe that within ten years our assessment of radiation-induced cancer should be quite precise.

REFERENCES

1. Lilienfeld, A. M. Practical limitations of epidemiological methods. *Environ. Health Perspect.* 52:3-8 (1983).
2. Upton, A. C. Environmental standards for ionizing radiation: theoretical basis for dose-response curves. *Environ. Health Perspect.* 52:31-40 (1983).
3. Beebe, G. W., Kato, H., and Land, C. E. Mortality experience of atomic bomb survivors 1950-1974: Life Span Study 8. Technical Report RERF TR 1-77, Radiation Effects Research Foundation, Hiroshima, 1977.
4. Court-Brown, W. M., and Doll, R. Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis. *Brit. Med. J.* 2: 1327-1332, (1965).
5. Radford, E. P. Human health effects of low doses of ionizing radiation: the BEIR III Controversy. *Radiat. Res.* 84: 369-394 (1980).
6. Boice, J. D., Jr., Land, C. E., Shore, R. E., Norman, J. E., and Tokunaga, M. Risk of breast cancer following low-dose exposure. *Radiology* 131: 589-597 (1979).
7. Modan, B., Ron, E., and Werner, A. Thyroid cancer following scalp irradiation. *Radiology* 123: 741-744 (1977).